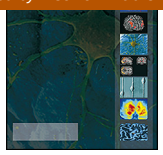
Neuroscience Letters 581 (2014) 46–51

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet



Paraoxonase 1 status and interactions between Q192R functional genotypes by smoking contribute significantly to total plasma radical trapping antioxidant potential

Chiara Cristina Bortolasci[a], Michael Maes[b,c,d], Heber Odebrecht Vargas[e], André Souza-Nogueira[a], Estefania Gastaldello Moreira[f], Sandra Odebrecht Vargas Nunes[e], Michael Berk[b,g,h,i], Seetal Dodd[b,g], Décio Sabbatini Barbosa[d,*]

[a] Laboratory of Graduation Research, State University of Londrina, Londrina, Paraná, Brazil
[b] Impact Strategic Research Centre, Deakin University, Geelong, Victoria, Australia
[c] Department of Psychiatry, Chulalongkorn University, Bangkok, Thailand
[d] Health Sciences Graduate Program, State University of Londrina, Londrina, Paraná, Brazil
[e] Department of Psychiatry, State University of Londrina, Londrina, Paraná, Brazil
[f] Department of Physiological Sciences, State University of Londrina, Londrina, Paraná, Brazil
[g] Department of Psychiatry, University of Melbourne, Parkville, Victoria, Australia
[h] Orygen Research Centre, Parkville, Australia
[i] Florey Institute for Neuroscience and Mental Health, Parkville, Australia

HIGHLIGHTS

- TRAP and PON1, 197 healthy, 91 with unipolar depression and 45 with bipolar disorder.
- PON1, male gender, RR genotype and body mass index are inversely correlated with TRAP.
- PON1 activity, interactions between PON1 Q192R genotypes and smoking influence TRAP.

ARTICLE INFO

Article history:
Received 5 June 2014
Received in revised form 5 August 2014
Accepted 11 August 2014
Available online 19 August 2014

Keywords:
Paraoxonase
Smoking
TRAP
Depression
Body mass index
Psychiatry

ABSTRACT

The measurement of the total radical trapping antioxidant potential (TRAP) is a general marker of peripheral blood antioxidant defenses. Paraoxonase 1 (PON1) is a potent antioxidant, which protects against lipid peroxidation. The study aimed to examine the relation between TRAP levels and PON1 activity, PON1 Q192R functional genotypes, smoking, interactions between PON1 genotypes and smoking, and mood disorders, while adjusting for effects of ethnicity, marital status, body mass index (BMI) and gender. The analyses were performed in 197 controls and 136 subjects with mood disorders. TRAP levels were significantly associated with higher plasma PON1 activity, the RR functional genotype, non smoking by RR carriers, male gender and a higher BMI. TRAP levels were significantly lower in patients with mood disorders than in controls, but this association was no longer significant after considering the effects of the above predictors. The risk in the subgroup with low TRAP levels is increased by a smoking X RR genotype interaction and decreased by male gender, the RR genotype, and higher BMI and PON1 activity. Plasma PON1 activity, the PON1 Q192R functional genotypes and specific interactions between this genotype and smoking contribute significantly to TRAP levels. Gender and BMI also appear to influence TRAP levels.

Abbreviations: ANCOVAs, analysis of covariance; ANOVAs, analysis of variance; ASSIST, alcohol, smoking and substance involvement screening; BD, bipolar disorder; BMI, body mass index; CMPA, 4-chloromethyl phenol acetate; DSM-IV, diagnostic and statistical manual of mental disorder; GLM, general linear analysis; HDL, high-density lipoprotein; HDRS, Hamilton depression rating scale; LDL, low-density lipoprotein; OS, oxidative stress; PA, phenyl acetate; PON1, paraoxonase 1; ROS, reactive oxygen species; SEM, standard error of the mean; TRAP, total radical trapping antioxidant potential; TUD, tobacco use disorder.

* Corresponding author at: Health Sciences Graduate Program – University Hospital, Av. Robert Koch 60, 86035-380 Londrina, Paraná, Brazil. Tel.: +55 43 3371 2451.
E-mail addresses: sabbatini2011@hotmail.com, sabatini@uel.br (D.S. Barbosa).

http://dx.doi.org/10.1016/j.neulet.2014.08.020
0304-3940/

1. Introduction

Cigarette smoke contains hundreds of compounds which act as pro-oxidants and produce reactive oxygen species (ROS). Smoking enhances oxidative stress (OS) and decreases antioxidant defense mechanisms [1]. Mood disorders, including major depression and bipolar disorder (BD), are accompanied by increased OS and lowered levels of antioxidants [2].

One major measure of total plasma antioxidant defense is the total radical trapping antioxidant potential (TRAP) in plasma [3]. An important antioxidant enzyme is paraoxonase 1 (PON1), which is lowered in individuals with mood disorders and tobacco use disorder (TUD) [4]. PON1 is an enzyme synthesized in the liver, and secreted into plasma where it is bound to high-density lipoprotein (HDL) particles. These protect against lipoprotein peroxidation, a key process underpinning the pathophysiology of atherosclerosis [5]. Polymorphisms of the PON1 gene determine PON1 enzymatic activities, e.g. the polymorphism with Q/R substitution at position 192 [4,5]. This functional Q192R polymorphism determines PON1 enzyme activity which in turn protects low-density lipoprotein (LDL) from oxidation. In this regard the Q192 alloenzyme is more efficient than the R192 aloenzyme [5].

The aim of this study is to examine whether TRAP levels are associated with PON1 status, smoking, mood disorders, interactions between the PON1 Q192R genotypes and smoking, ethnicity, marital status, body mass index (BMI) and gender.

2. Subjects and methods

2.1. Subjects

The participants were 197 normal controls, 91 patients with major depression and 45 with BD recruited at the State University of Londrina. Participants of Caucasian, Asian, African and mixed ethnicities, aged 18–65 years, were enrolled in this study. The diagnoses of BD, depression and tobacco use disorder (TUD, current smokers) were made using a validated Portuguese version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [6]. All TUD subjects were current smokers who at the time of interview reported smoking every day or some days. Mood disorder patients in the acute phase of illness and in partial or total remission were included. Subjects with diagnoses other than depression and BD (e.g. schizophrenia, substance abuse disorders, and psycho-organic syndromes) were excluded. Normal controls were individuals without a lifetime or current diagnosis of axis I.

We excluded individuals with abnormal values of hemogram, aspartate transaminase, alanine transaminase, urea, creatinine; who suffered from diabetes, (auto)immune disorders, chronic obstructive pulmonary disorder, inflammatory bowel disease, and neuroinflammatory disorders; who were treated with immunomodulatory drugs or antioxidant supplements.

The severity of depression was measured using a validated Portuguese version of the Hamilton Depression Rating Scale (HDRS) [7]. The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) was used to assess risk levels of alcohol use [8]. BMI was calculated as weight (kg)/body height (in meter)^2. The study was approved by the Research Ethics Committee (number 250/2010). All participants gave written informed consent prior to participating in this study.

2.2. Laboratory assessments

Blood was sampled after an overnight fast. TRAP was measured by chemiluminescence in an adaptation of the method described by Repetto et al. (1996) [9]. A comparison of the induction time after the addition of known concentrations of Trolox and plasma is used to measure TRAP values of Trolox equivalents.

PON1 status was determined as described by Richter et al. (1999) [10]. 4-Chloromethyl phenol acetate (CMPA) hydrolysis and phenyl acetate (PA) hydrolysis under high salt conditions was measured in a microplate spectrophotometer. The results obtained with these two assays were used to plot a 2-dimensional enzyme activity graphic that displays rates of arylesterase activity under high salt conditions versus CMPase activity. Since the polymorphism Q192R confers differential catalytic activity against these two substrates, the plot splits the population into the three functional positions 192 genotype (QQ, QR and RR). Measurement of PA hydrolysis at low salt concentrations reveals plasma PON1 activity since at this condition PON1 Q192R polymorphism does not influence PON1 catalytic activity against PA [10].

2.3. Statistics

Analyses of variance (ANOVAs) and covariance (ANCOVAs) were performed to examine differences between treatments means followed by Tukey's test. Analyses of contingency tables (χ^2 tests) were performed to ascertain differences in the distribution of variables between diagnostic categories. Relationships between variables were checked using Pearson's correlation coefficients and stepwise General linear model (GLM) analyses. We used automatic stepwise binary logistic regression analyses to examine the associations between patients with lower TRAP levels (versus higher TRAP levels, median-split dichotomized) as dependent variable and different explanatory variables, including PON1 status, smoking, BMI, gender, etc. The data were analyzed using SPSS and the statistical significance set at $\alpha = 0.05$ (two tailed).

3. Results

3.1. Plasma TRAP measurements

Table 1 shows that TRAP levels were significantly lower in women than in men. There were no significant associations between TRAP levels and ethnicity or marital status. Patients had significantly lower plasma TRAP levels than controls. TUD patients had significantly lower TRAP levels than non-smokers. There were no significant differences in TRAP values between QQ, QR and RR carriers.

In the total study group, there were no significant correlations between plasma TRAP levels and age ($r = -0.003$, $p = 0.952$, $n = 333$), years of education ($r = 0.059$, $p = 0.286$, $n = 333$), and alcohol use ($r = 0.082$, $p = 0.137$, $n = 332$). There were significant correlations between plasma TRAP and PON1 activity ($r = 0.125$, $p = 0.022$, $n = 333$), BMI ($r = 0.202$, $p < 0.001$, $n = 333$) and HDRS ($r = -0.200$, $p < 0.001$, $n = 332$).

Table 2 shows the results of GLM analyses with TRAP as dependent variable and age, BMI, years of education, plasma PON1 activity, HDRS, use of alcohol, gender, smoking, PON1 Q192R genotypes (entered as QQ + QR versus RR), diagnosis (entered as controls versus patients or as controls versus depression versus BP disorder), marital status, and ethnicity as explanatory variables. 28.4% of the variance in plasma TRAP levels was explained by PON1, the interaction smoking by PON1 Q192R genotypes, BMI and gender ($F = 16.03$, $df = 8/324$, $p < 0.001$). PON1, BMI, male gender and the RR genotype were significantly associated with increased TRAP levels. TRAP was significantly higher in RR than in QQ ($p = 0.009$) and QR ($p = 0.024$) carriers, but there were no significant differences between QQ and QR carriers ($p = 0.642$). The interaction pattern showed that non smoking in subjects with a RR and

Table 1
Measurements of total radical trapping antioxidant potential (μM Trolox) in 333 subjects.

Variables	Type	*n*	Mean (SD)	*F*	*df*	*p*
Gender	Men	115	901.4 (132.6)	60.43	1/331	<0.001
	Women	218	785.3 (138.2)			
Ethnicity	Caucasian	228	825.6 (138.6)	0.46	2/330	0.634
	African Asian	50	838.2 (126.6)			
	Mixed	55	812.8 (134.0)			
Marital status	Single	49	834.6 (119.5)	0.17	2/330	0.845
	Stable	221	825.0 (141.2)			
	Separated, widowed	63	819.7 (130.6)			
Diagnosis	Controls	197	839.6(136.5)	5.43	1/331	0.020
	Mood disorders	136	804.9 (132.9)			
Diagnosis	Controls	197	839.6 (136.5)	2.75	2/330	0.065
	Depression	91	808.2 (136.8)			
	Bipolar disorder	45	798.1 (125.8)			
TUD	No	190	837.7 (133.2)	4.05	1/331	0.045
	Yes	143	809.1 (138.2)			
PON1 Q192R Genotypes	QQ QR RR	151	822.0 (127.7)	1.36	2/330	0.258
		132	817.9 (140.9)			
		50	855.4 (144.9)			

Mood disorders: depression and bipolar disorder.
TUD: tobacco use disorder.

Table 2
Results of general linear model analysis with total radical trapping antioxidant potential as dependent variable and the listed variables as explanatory variables.

Variables	*F*	*df*	*p*	*η*
Plasma PON1	5.87	1/324	0.016	0.018
Smoking X PON1 Q192R genotypes	3.76	5/324	0.003	0.055
Body mass index	26.59	1/324	<0.001	0.076
Gender (male)	88.45	1/324	<0.001	0.214

PON1: paraoxonase 1.
PON1 Q192R genotypes: entered as QR and RR genotypes with QQ as reference group.
η: partial η^2.

QR genotype is associated with increased TRAP levels: TRAP levels were significantly higher in non-smokers than in smokers in QR (adjusted mean ± SEM = 875.0 ± 14.3 versus 806.7 ± 15.4 μM Trolox) and RR (906.3 ± 25.5 versus 863.6 ± 21.9 μM Trolox) carriers (the means were obtained by GLM analysis after adjusting for the abovementioned background variables). There were no differences in TRAP between QQ smokers (833.0 ± 16.0 μM Trolox) and QQ non smokers (835.2 ± 12.3 μM Trolox). All other variables were not significant in this regression analysis including diagnostic classifications. In addition, forced entry of the three diagnostic groups (depression, bipolar disorder and controls) showed that these diagnostic groups were not significant in predicting TRAP ($F = 1.20$, $df = 2/322$, $p = 0.301$), while PON1 ($F = 6.11$, $df = 1/322$, $p = 0.014$), smoking X PON1 Q192R genotypes ($F = 3.60$, $df = 5/322$, $p = 0.004$), BMI ($F = 28.15$, $df = 1/322$, $p < 0.001$) and gender ($F = 84.30$, $df = 1/322$, $p < 0.001$) remained significant in predicting TRAP. ANOVA showed that in TUD subjects, TRAP was not significantly different ($F = 1.56$, $df = 2/140$, $p = 0.213$) between QQ (mean ± SD = 822.9 ± 109.9 μM Trolox, $n = 54$), QR (785.4 ± 146.8 μM Trolox, $n = 60$) and RR individuals (832.2 ± 162.6 μM Trolox, $n = 29$).

We examined the effects of psychotropic drugs on our results. There were no significant differences ($F = 0.08$, $df = 1/331$, $p = 0.775$) in TRAP levels between subjects without (mean ± SD 824.6 ± 135.7 μM Trolox, $n = 296$) and with psychotropic drug use (831.4 ± 139.7 μM Trolox, $n = 37$). We re-ran the above GLM analysis in subjects who were drug free. 30% of the variance in TRAP was explained ($F = 15.38$, $df = 8/287$, $p < 0.001$) by PON1 ($F = 4.63$, $df = 1/287$, $p = 0.016$), smoking X PON1 Q192R genotypes ($F = 3.05$, $df = 5/287$, $p = 0.011$), BMI ($F = 29.78$, $df = 1/287$, $p < 0.001$) and gender ($F = 81.61$, $df = 1/287$, $p < 0.001$).

3.2. Characteristics of subjects with low versus high plasma TRAP levels

We dichotomized the study group into two equal groups using 818.80 μM Trolox as threshold value. Table 3 lists the characteristics of subjects with lowered versus higher TRAP levels. There were no significant differences in age, ethnicity, marital status, diagnosis, smoking, PON1 Q192R genotypic distribution, plasma PON1 activity and years of education between the two study groups. Subjects with lower TRAP levels showed a higher frequency of females and a lower BMI than subjects with higher TRAP levels.

Table 4 shows the results of an automatic stepwise logistic regression analysis with the low TRAP subgroup as dependent variable (<818.80 μM Trolox) and all variables listed in Table 3 and the interaction pattern smoking X PON1 Q192R genotypes as explanatory variables. We found that using five predictors, 67.3% of all cases were correctly classified (sensitivity = 70.7% and specificity = 63.9%; $\chi^2 = 72.61$, $df = 5$, $p < 0.001$; Nagelkerke = 0.261). PON1, male gender, BMI and the RR genotype were inversely associated with the lower TRAP subgroup, whereas the interaction smoking by RR carriers increased the risk to belong to the low TRAP group.

4. Discussion

The findings of this study are that TRAP was significantly related to plasma PON1 activity, PON1 Q192R genotypes, an interaction between smoking and these genotypes, BMI and gender. In addition, subjects with mood disorders displayed lowered TRAP levels than controls, although these effects were not significant in the final regression analysis. TUD subjects showed lower levels of TRAP than controls, but these effects were no longer significant after

Table 3
Characteristics of subjects divided into those with lower versus higher (median-dichotomized) total radical trapping antioxidant potential (TRAP) levels.

Variables	Type	Lower TRAP ($n = 167$)	Higher TRAP ($n = 166$)	F or $X2$	df	p
TRAP (μM)Trolox)	–	718.3 (±76.6)	933.1(±89.4)	544.95	1/331	<0.001
Gender	Men Women	31136	8482	37.80	1	<0.001
Age (years)	–	46.3 (±8.2)	46.4 (±8.6)	0.00	1/331	0.946
Ethnicity	Caucasian African Asian Mixed	1132331	1152724	1.22	2	0.542
Marital status	Single Stable Separated + widowed	2410736	2511427	1.52	2	0.467
Diagnosis	Controls Mood disorders	9176	10660	30.2	1	0.082
Diagnosis	Controls Depression BD	914828	1064317	4.41	2	0.129
TUD	No Yes	9077	10066	1.37	1	0.242
PON1 Q192R Genotypes	QQ QR RR	787019	736231	3.53	2	0.171
Plasma PON1 (U/mL)		188.6 (±56.8)	196.1(±52.2)	1.55	1/331	0.213
BMI (kg/m^2)	–	26.03 (±4.84)	27.86(±4.74)	12.20	1/331	0.001
Education (years)	–	13.3 (±5.5)	13.6 (±6.8)	0.12	1/331	0.723

Results are shown as mean (±SD).
Results of analyses of variance (F) or analyses of contingence tables (X^2 tests).
BD: bipolar disorder.
TUD: tobacco use disorder.
BMI: body mass index.

considering the interaction between current smoking and PON1 Q192R genotypes. TRAP levels were significantly associated with higher plasma PON1 activity. PON1 is a HDL-associated enzyme with multifunctional activities including antioxidant properties [11]. Therefore, our findings confirm that this enzyme plays a role as one of the antioxidants contributing to total TRAP levels.

The RR functional genotype was associated with higher TRAP levels. These findings corroborate those of previous papers that the RR genotype is more protective against OS and that the QQ genotype increases susceptibility to genotoxicity [12]. The Q isoform is associated with a lowered protective activity against LDL and HDL oxidation and reduced paraoxon hydrolyzing activity [13]. Given the role of OS in aging, it is also interesting to note that QR and RR carriers have a better survival advantage than Q allele carriers and those patients with a QQ genotype have worse diabetes control than those with a RR genotype [14]. All in all, our data suggest that RR individuals are more protected than QQ carriers against OS.

We found that smoking decreased TRAP levels in RR and QR carriers. Thus, smoking has a stronger effect on antioxidant defenses in RR and QR individuals than in QQ individuals. Chronic smoking is related to depletion of antioxidant levels [15], total plasma antioxidant capacity and PON1 plasma activity [16]. Moreover, the acute effects of smoking also result in increased lipid peroxidation [17]. Our study however shows that the genotype-smoking interaction explained more of the variance in plasma TRAP levels than smoking alone, suggesting that the effects of smoking on total plasma TRAP levels are attributable to the effects in QR and RR carriers only. Future research should delineate whether the effects of smoking enhancing oxidative biomarkers and decreasing specific antioxidants are mediated by interactions between smoking and PON1 Q192R genotypes.

Our results showed that TRAP levels were significantly higher in males than in females. These results extend findings that women may show higher levels of OS than men [18]. For example, in a study sample of normal volunteers and patients with chronic fatigue, we found significantly higher plasma peroxide levels in women than in men [18]. Such differences may be associated with the lower plasma TRAP levels in women observed in our study. In preclinical experiments of peripheral tissue antioxidant defenses were higher in female than in male rats, while brain lipid peroxidation was higher in males than in females [19]. Higher levels of vitamin E and elevated activity of glutathione peroxidase were detected in females [20–22]. Estrogens have significant antioxidant properties, although the exact mechanisms by which estrogens exert this action remain unknown [23–25].

We found decreased TRAP levels in patients with mood disorders (either depression or BD) compared to controls. Moreover, there was an inverse correlation between TRAP and severity of depression. Those results corroborate previous data that mood disorders are accompanied by lowered antioxidant levels, either total plasma antioxidant activity or specific antioxidants and increased OS [2,26–28]. The differences between patients with mood

Table 4
Results of automatic stepwise logistic regression analysis with lower versus higher (median-dichotomized) TRAP levels (higher plasma TRAP as reference group) as dependent variable and the listed variables as predictors.

Variables	Wald	df	p	Odds ratio	CI lower	CI upper
Plasma PON1	4.61	1	0.032	0.39	0.16	0.92
PON1 Q192R genotypes	9.55	1	0.002	0.15	0.05	0.51
Smoking (1) X PON1Q192R genotype	5.62	1	0.018	5.42	1.34	21.91
Body mass index	18.39	1	<0.001	0.89	0.84	0.94
Gender (male)	41.78	1	<0.001	0.17	0.10	0.29

CI: 95% confidence intervals.
PON1 Q192R genotypes: paraoxonase1 Q192R genotypes, QQ + QR versus RR.

disorders and normal controls, however, were no longer significant after considering the effects of the other variables, suggesting that the association between mood disorders and TRAP levels are mediated by other variables.

Surprisingly, the results of this study show that plasma TRAP levels are significantly and positively correlated to BMI. In the ATTICA study, on the other hand, obese and overweight males and females showed lower total antioxidant capacity concentrations as compared to normal weight individuals [29]. In accordance with the ATTICA study, the Framingham offspring cohort, in which a series of laboratory assessments, obesity measures, OS and cardiovascular risk factors were measured, showed that obesity, particularly central obesity, was an independent positive predictor for systemic OS [30]. Obesity is known to increase OS in normal volunteers and clinical populations of all ages as indicated by increased lipid peroxidation [31]. Abdominal and hepatic fat increases lipid peroxidation through excess of free fatty acids, lipoprotein-bound lipids and cytokines [32]. Nevertheless, TRAP levels mainly reflect the antioxidant potential of urate (35–65%). There is evidence that uric acid is significantly related to the BMI [33]. Therefore, our findings that plasma TRAP levels are related to BMI may be explained by the effects of uric acid, which is positively associated with BMI.

This study has strengths and limitations which need to be noted in interpreting the results. In the present study, we controlled statistically for effects of ethnicity, drug state, including use of psychotropic medication and statins, and use of alcohol. A first limitation is that this study is cross sectional and therefore no deductions can be made on causal relationships. A follow-up study should be carried out to delineate the interrelationships between TRAP plasma levels and uric acid, on the one hand, and BMI and gender, on the other. Lastly, in this study we examined the effects of current TUD defined as patients with nicotine dependence who were current smokers. Thus, our study design does not allow examination of the chronic versus acute effects of smoking tobacco.

In conclusion, TRAP levels are significantly predicted by higher plasma PON1 activity, the RR functional genotype, non smoking by RR carriers, gender and BMI. Plasma PON1 activity, PON1 genotypes and an interaction between PON1 Q192R genotypes and TUD contribute significantly to plasma TRAP levels, independently of the effects of gender and BMI.

Funding

This study was supported by Araucária Foundation (PPSUS 200/2010 - Protocol 19544).

Acknowledgements

The authors wish to thank the Centre of Approach and Treatment for Smokers, Molecular Genetics Laboratory, and Clinical Immunology section of University Hospital of Londrina. C.C.B. is supported by CAPES, Scholarship BEX 12745/13-8. M.B. is supported by a NHMRC Senior Principal Research Fellowship 1059660. M.M. is supported by a CNPq – PVE fellowship and the Health Sciences Graduate Program fellowship, State University of Londrina.

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